UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

Actelion Pharmaceuticals, Ltd., Plaintiff, v. Sun Pharmaceutical Industries, Inc., *et al.*, Defendants.	Civil Action No. 3:17-cv-5015 (PGS) (DEA) **MEMORANDUM**

SHERIDAN, U.S.D.J.

This matter comes before the Court on joint claim construction submitted by plaintiff Actelion Pharmaceuticals, Ltd., and defendants Sun Pharmaceutical Industries, Inc., and Sun Pharmaceutical Industries, Ltd., concerning United States Patent No. 8,598,227 ("'227 patent"). The '227 patent is listed to market and sell the drug Veletri,® a treatment which improves exercise capacity for individuals suffering from pulmonary arterial hypertension (PAH). The parties dispute the meaning of "alkalinizing agent," as used in the '227 patent. The Court held a *Markman* hearing on November 13 and 14, 2018. The sole claim construction issue is whether Actelion disclaimed glycine from its definition of "alkalinizing agent" in statements it made to distinguish prior art during the prosecution of a divisional patent.

BACKGROUND

PAH is a disease characterized by high blood pressure in the lungs, which causes shortness of breath, fatigue, and chest pain in those afflicted, and ultimately results in death from ventricular failure. (Declaration of Preston K. Ratliff II ("Ratliff Decl."), Ex. 2, Humbert et al., Treatment of Pulmonary Arterial Hypertension, N. Engl. J. Med. 351;14 (Sept. 30, 2014) ("Humbert"), at 1425-26). Epoprostenol, also known as prostacyclin, is a naturally occurring prostaglandin which dilates blood vessels and inhibits platelet aggregation. (Ratliff Decl., Ex. 5, Flolan Product Information, at 1).

On August 28, 1980, two inventors filed an application for a United States Patent, which ultimately issued as U.S. Patent No. 4,335,139 ("the Watts Patent"). (*See* Declaration of Paul N. Harold (Harold Decl.), Ex. I, United States Patent No. 4,335,139). The Watts patent claims:

> A pharmaceutical formulation comprising an active compound selected from prostacyclin, 15-methyl-prostacyclin, 16, 16-dimethylprostacyclin or a pharmaceutically acceptable salt of any one of those in association with a pharmaceutically acceptable buffer having a pH of at least 9 and based on a pharmaceutically acceptable amino acid as a buffering acid as a buffering acid in the buffer and, optionally, a further pharmaceutically acceptable carrier.

(*Id.* at 8:35 to 43). The invention claimed by the Watts Patent had an "antiaggregatory effect on blood platelets" and was "useful, for example, in preventing or mitigating the formation of thrombi or emboli during extra corporeal circulation of blood." (*Id.* at 1:16 to 19).

Although "[i]ntravenous prostacyclin (epoprostenol) was first used to treat primary pulmonary hypertension in the early 1980s," it was first approved by the FDA for treatment of PAH in 1995, and subsequently marketed by GlaxoSmithKline as Flolan. (Ratliff Decl., Ex. 2, Humbert, et al., *Treatment of Pulmonary Arterial Hypertension*, N. Engl. J. Med. 2004; 351:1425-36 (Sept. 30, 2004); Ex. 1, U.S. Patent Number 8,598,227 ("'227 Patent")). Flolan consists of "epoprostenol sodium equivalent to either 0.5 mg . . . or 1.5 mg . . . epoprostenol, 3.76 mg glycine,

2.93 mg sodium chloride, and 50 mg mannitol." (*Id.*). Clinical studies have shown that epoprostenol improves exercise tolerance, hemodynamics, and long-term survival, and can render lung transplants unnecessary in patients with severe forms of PAH. (*Id.* at 6-7; Ratliff Decl., Ex. 2, Humbert et al., at 1430).

However, some considered Flolan-brand epoprostenol, with a half-life of just several minutes, to be highly unstable; it was administered by continuous infusion via a portable pump connected to a catheter permanently tunneled into the patient's subclavian vein. (Ratliff Decl., Ex. 2, Humbert et al., at 1430). Flolan is a freeze-dried product, which is reconstituted using a proprietary sterile diluent prior to its infusion. (Ratliff Decl., Ex. 5, Flolan Product Information, at 7, 20-21, 28). The sterile diluent for Flolan "is supplied in 50-mL glass vials containing 94 mg glycine, 73.5 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP." (*Id.* at 1). One reservoir of reconstituted Flolan could be stored in refrigerated conditions for no more than forty hours and administered at room temperature for only eight hours. (*Id.* at 27-28).

Nagesh Palepu, an inventor, later discovered "that epoprostenol in the presence of an alkalinizing agent, and high pH . . . is very stable compared to Flolan." (Ratliff Decl.), Ex. 1, '227 Patent, at 4:15 to 18). The new formulation, marketed as Veletri®, allows epoprostenol to be stored in refrigerated conditions for up to eight days and remains stable at room temperature for forty-eight to seventy-two hours. (Ratliff Decl., Ex. 4, Veletri Highlights of Prescribing Information, at 4-5).

In 2006, Palepu filed a provisional application with the Patent and Trademark Office (PTO) titled "Novel Epoprostenol Formulation and Method of Making Thereof." (Declaration of Paul N. Harold (Harold Decl.), Ex. C., Provisional Patent Application Nos. 60/783,429, 60/772,563, and

60/764,769). The '227 patent, a division of the 2006 application, names Actelion as assignee. (*See* '227 Patent, at cover (60)). The patent examiner restricted that prior application because it contained three "groups of inventions": (1) "a method of making a composition"; (2) "a composition"; and (3) "a method of treating a patient." (Harold Decl., Ex. F, May 7, 2010 Office Action Summary, at 2). The examiner required Actelion "to elect a single invention to which the claims must be restricted." (*Id.*).

'802 Patent

Actelion elected to prosecute the "composition" claims in a divisional application that would result in United States Patent Number 8,318,802 (the '802 patent). (Harold Decl., Ex. G, Response to Restriction Requirement). By way of background, Actelion's initial application sought to claim:

> Claim 16 (Previously Presented): A pharmaceutical composition comprising:
> (a) epoprostenol or a salt thereof; and
> (b) *an alkalinizing agent*,
> wherein when the composition is reconstituted, the pH of the reconstituted solution is greater than 11.
>
> . . . .
>
> Claim 19 (Original): The composition of claim 16, wherein the *alkalinizing agent* is selected from the group consisting of *arginine*, lysine, meglumine, N-methyl glucosomine, *an amino acid with a pKa of 9.0 and above*, trisodium phosphates, sodium carbonates, and tetrasodium-EDTA.

(*Id.* at 4-5 (emphasis added)). The examiner rejected that initial application noting that prior art "teaches stabilized formulations of prostacyclin (which is also known as epoprostenol) with an amino acid and a base . . . and they further specify glycine and arginine as amino acids to be used as buffers." (Harold Decl., Ex. H, August 17, 2010 Office Action Summary, at 4). The examiner found the claims "fail[ed] to particularly point out and distinctly claim the subject matter which

applicant regards as the invention" because, as to claim 19, "[a]rginine is claimed as an alkalinizing agent . . . and glycine is an amino acid with a pKa above 9 and thus they teach compositions comprising both prostacyclin/epoprostenol and an alkalinizing agent." (*Id.* at 4-5). The examiner also noted that claim 16 "would not require any specific pH in the composition." (*Id.* at 4). In other words, she concluded the claimed invention was insufficiently distinct from the prior art.

Actelion submitted another response with, in pertinent part, the following amendments:

> Claim 16 (Currently amended): A pharmaceutical composition that is capable of being reconstituted with a conventional intravenous fluid to a pH greater than 12 comprising:
> (a) epoprostenol or a salt thereof; ~~and~~
> (b) ~~an alkalinizing agent~~ arginine; and
> (c) an inorganic base selected from the group consisting of sodium hydroxide and potassium hydroxide~~;~~
> ~~wherein when the composition is reconstituted, the pH of the reconstituted solution is greater than 11~~.
>
> . . . .
>
> Claim 19 (Currently amended): The composition of claim 16, wherein the ~~alkalinizing agent is selected from the group consisting of arginine, lysine, meglumine, N-methyl glucosomine, an amino acid with a pKa of 9.0 and above, trisodium phosphates, sodium carbonates, and tetrasodium EDTA~~ composition is capable of being reconstituted with a conventional intravenous solution to a pH of 13 or higher.

(Harold Decl., Ex. J, Response Under 37 C.F.R. 1.111, at VELET_00000446 to 447). Actelion noted in its response to the examiner that "there is no disclosure in [the prior art] of a composition having a pH greater than 12, or alternatively 13 or higher, as required by the present claims" and thus "respectfully submit[ted] that the rejection . . . be withdrawn." (*Id.* at VELET_00000454). Actelion also explained in its response to the examiner that:

> The present invention claims a) a pharmaceutical composition comprising epoprostenol or a salt thereof; and b) a stable epoprostenol solution. All of said claims are limited in the following way: a) arginine as alkalinizing agent is used, b) the pH of the solution is higher than 12, and c) inorganic base from the group

> consisting of sodium hydroxide and potassium hydroxide are used to reach the high pH.

(*Id.* at VELET_00000457). Further distinguishing the prior art, Actelion stated:

> Applicants respectfully submit that a person of ordinary skill in the art, reading Watts et al., would not consider arginine as amino acid for high pH epoprostenol formulations since Watts et al. focuses on epoprostenol formulations comprising glycine . . . and that the commercial epoprostenol formulations Flolan® . . . comprises glycine as amino acid . . . .

(*Id.* at VELET_00000459). Actelion thereby distinguished its product, Veletri, by narrowing the alkalinizing agent to arginine; increasing the pH to 13; and specifying which base was used to increase the pH.

The examiner again rejected the claim, (Harold Decl., Ex. K, April 18, 2011 Office Action Summary), but Actelion argued that although there was a prima facie showing of obviousness, it had "clearly shown . . . the unexpected improved stability between the compositions of the instant invention and those of the prior art," which should permit the applicant to overcome the examiner's rejection, (Harold Decl., Ex. L, Amendments and Response 37 C.F.R. 1.111, at 9); *see In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (explaining the unexpected results doctrine). Distinguishing Flolan, Actelion noted:

> The compositions of the instant invention as represented in Batch #'s EPP-7, 10, 13, 26 and 38 formed from a bulk solution containing epoprostenol and arginine with a pH of greater than 12 are superior to those formed from bulk solution containing epoprostenol and glycine with a pH of 10.5 (Batch # EPP-8).

(*Id.*; *see also id.* at 11). Actelion also specified that "the results show that a lower pH, epoprostenol degrades almost completely at one month at 40°C while at a higher pH, the stability improves dramatically." (*Id.* at 10). Ultimately, after requiring additional minor amendments, the examiner allowed the claims, and claim 16, as amended, became claim 1 of the '802 patent. (Harold Decl., Ex. O, Notice of Allowance and Fee(s) Due; Harold. Decl., Ex. A, The '802 Patent).

'227 Patent

After the '802 patent was successfully prosecuted, Actelion filed another divisional application for both the "method of making a composition" and "method of treating a patient"; claims that had been omitted from the '802 patent. (Harold Decl., Ex. P, September 17, 2012 Supplemental Amendments). The method-of-making claims reintroduced the term "alkalinizing agent":

> Claim 54 (New): A method for making an epoprostenol composition comprising the steps of:
>
> (a) Providing a bulk solution comprising (i) epoprostenol or a salt thereof; and (ii) an alkalinizing agent; and
>
> (b) Adjusting the pH of the bulk solution to greater than 13.

(*Id.* at 3 *see also id.* at 4 (claims 60, 61)). However, the corresponding treatment-related claim referenced the more narrow "arginine." (*Id.* at 5 (claim 69), 6 (claim 75)). The examiner initially rejected the application, requiring Actelion to restrict it to either the composition claims or the treatment claims. (Harold Decl., Ex. Q, March 12, 2012 Office Action Summary, at 2-3). He also stated that the term "alkalinizing agent" comprises compounds that "are structurally and chemically distinct from each other compound within their species group" and instructed Actelion to elect "a specific [a]lkalinizing agent species (e.g., arginine)." (*Id.* at 4). Actelion submitted a response electing "with traverse" the treatment-related claims, (Harold Decl., Ex. R, April 12, 2013 Response to Restriction Requirement), but filed a "Supplemental Amendment" that did not address either concern raised by the examiner, (*see* Harold Decl., Ex. S, Supplemental Amendments to April 12, 2013 Response). The examiner allowed Actelion's claims without any reference to its failure to respond to the restriction requirement. (*See* Harold Decl., Ex. T, Notice of Allowance and Fee(s) Due, at 1). At oral argument, counsel for Actelion stated that it met with

the examiner prior to the approval and subsequent to "amend[ing] the method-of-making claims to recite the pH range of greater than 13." (Oral Argument Tr. at 29:4 to 8).

The '227 patent also discloses the following definition of "alkalinizing agent":

> An alkalinizing agent, as used herein, means an agent that provides alkaline environment (pH>7) when epoprostenol is dissolved in water along with the alkalinizing agent. Additionally, although the alkalinizing agent provides an alkaline environment, it does not contain a basic hydroxide group, but may contain at least one functional group that accepts a proton from water when dissolved in water or water/organic solvents mixture. The alkalinizing agent should have at least one pKa greater than 9.0. Preferably, the alkalinizing agent is in solid phase and is soluble in an aqueous medium. The alkalinizing agents may be, but are not limited to, arginine, lysine, meglumine, N-methyl glucosomine, *any other amino acid with a pKa of 9.0 and above*, alkaline phosphates such as trisodium phosphates, inorganic carbonates such as sodium carbonates, sodium salts of carboxylic acids such as tetrasodium-EDTA, or combinations thereof. *The most preferred alkalinizing agents are arginine and sodium carbonate.*
>
> In certain embodiments, the alkalinizing agent may be common buffers including, but not limited to, various salt, acidic, or basic forms of the following anions: citrate, phosphate, tartrate, succinate, adipate, maleate, lactate, acetate, bicarbonate, pyruvate, and carbonate. Representative salts of these buffers which may be used are the sodium and potassium forms, as long as the salt and the amount are physiologically compatible in an injectable composition. Mixtures of these buffering agents may also be used.

(Ratliff Decl., Ex. 1, The '227 Patent, at 5:3 to 29 (emphasis added)).

Veletri was launched in the United States in 2010 as a treatment for PAH. (Ratliff Decl., Ex 4, Veletri Highlights of Prescribing Information, at 20-21). On May 26, 2017, Sun notified Actelion that it had filed an abbreviated new drug application seeking approval to market a generic version of Veletri. (Ratliff Decl., Ex. 8, May 26, 2017 Notice Letter).

LEGAL STANDARD

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312

(Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). Claim construction determines the correct claim scope and is a determination exclusively for the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978-79 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The focus in construing disputed terms in claim language "is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *Id.* at 986.

To determine the meaning of the claims, courts start by considering the intrinsic evidence. *Phillips*, 415 F.3d at 1313; *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 861 (Fed. Cir. 2004); *Bell Atl. Network Servs., Inc. v. Covad Comms. Group, Inc.*, 262 F.3d 1258, 1267 (Fed. Cir. 2001). The intrinsic evidence includes the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1314; *C.R. Bard, Inc.*, 388 F.3d at 861.

"[C]laims 'must be read in view of the specification of which they are a part.'" *Id.* at 1315 (quoting *Markman*, 52 F.3d at 979). "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). This is true because a patentee may define his own terms, give a claim term a different meaning than the term would otherwise possess, or disclaim or disavow the claim scope. *Id.* at 1316. In these circumstances, the inventor's lexicography governs. *Id.* But, "[a]lthough the specification may aid the court in interpreting the meaning of disputed claim language, particular embodiments and examples appearing in the specification will not generally be read into the claims." *Comark Commc'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998) (quoting *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988)); *see also Phillips*, 415 F.3d at 1323 ("[A]lthough the specification often describes very specific

embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments.").

Prosecution history is another tool to supply the proper context for claim construction. It "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower that it would otherwise be." *Phillips*, 415 F.3d at 1317. "The prosecution history . . . consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent." *Id.*

In addition, "statements made by the inventor during continued prosecution of a related patent application can, in some circumstances, be relevant to claim construction." *Ventana Med. Sys., Inc. v. Biogenix Labs, Inc.*, 473 F.3d 1173, 1184 (Fed. Cir. 2006). "This is particularly so where 'the prosecution history of one patent is relevant to an understanding of the scope of a common term in a second patent stemming from the same parent application.'" *Medeva Pharm. Suisse A.G. v. Par Pharm., Inc.*, 2012 WL 1981821, at *7 (D.N.J. June 1, 2012) (quoting *Microsoft Corp. v. Multi-Tech. Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004)). "[S]tatements made during the continued prosecution of [an ancestor or] a sibling application may 'inform the meaning of the claim language by demonstrating how the inventor understood the invention.'" *Ventana*, 473 F.3d at 1184 (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1371 (3d Cir. 2005).

Overall, in construing the claims, "[t]he judge's task is not to decide which of the adversaries is correct. Instead, the judge must independently assess the claims, the specification, and if necessary the prosecution history and relevant extrinsic evidence, and declare the meaning of the claims." *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1556 (Fed. Cir. 1995).

ANALYSIS

Sun does not dispute that the definition of alkalinizing agent, as used in the '227 patent specifications, would include glycine under a plain meaning analysis. Indeed, included in the definition of alkalinizing agent is "any other amino acid with a pKa of 9.0 and above," ('227 Patent at 5:15-16), and, as noted by the first patent examiner, "glycine is an amino acid with a pKa above 9." (Harold Decl., Ex. H, August 17, 2010 Office Action Summary at 4-5). Rather, Sun argues that Actelion's statements and conduct in prosecuting the '802 patent disclaimed glycine from the definition of "alkalinizing agent" in the '227 patent.

Prosecution Disclaimer

Where a "patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003). A disavowal precludes a patentee from protection where the "patentee advises the examiner (and the public after patent issuance) that a particular structure is not within his invention." *Id.* at 1325.

To constitute a disavowal, the patentee's position taken before the PTO must "lead a competitor to believe that the applicant had disavowed coverage of the relevant subject matter." *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002). "Consequently, for prosecution disclaimer to attach, . . . precedent requires that the alleged disavowing actions or statements made during prosecution be both clear and reasonable." *Id.* When an applicant is alleged to have made "a binding disavowal of claim scope in the course of prosecution the patent, through arguments made to distinguish prior art references," the disavowal

must "constitute clear and unmistakable surrenders of subject matter." *Cordis Corp. v. Medtronic Ave., Inc.*, 511 F.3d 1157, 1177 (Fed. Cir. 2008).

"It is well settled that 'prosecution disclaimer may arise from disavowals made during the prosecution of ancestor patent applications.'" *Heuft Systemtechnik GMBH v. Indus. Dynamics Co. Ltd.*, 282 Fed. App'x 836, 841 (Fed. Cir. 2008) (quoting *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1333 (Fed. Cir. 2007)). Although "the prosecution of one claim term in a parent application will generally not limit different claim language in a continuation application," an exception applies "where an amendment to a related limitation in the parent application distinguishes prior art and thereby specifically disclaims a later (though differently worded) limitation in the continuation application." *Invitrogen Corp. v. Clongen Labs., Inc..*, 429 F.3d 1052, 1078 (Fed. Cir. 2005). Likewise, "[w]hen the application of prosecution disclaimer involves statements from prosecution of a familial patent relating to the same subject matter as the claim language at issue in the patent being construed, those statements in the familial application are relevant in construing the claims at issue." *Ormco Corp.*, 498 F.3d at 1333.

Similar to the prosecution history of the patent in suit, statements limiting a related term in a parent application "constitute[] a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to rely on those representations when ascertaining the degree of lawful conduct, such as designing around the claimed invention." *Hockerson-Halberstadt, Inc. v. Avia Group Intern., Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000). "Claims must not be construed in one way in order to obtain their allowance and in a different way against accused infringers." *Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995); *See also Springs Window Fashions, LP v. Novo Indus., LP*, 323 F.3d 989 (Fed. Cir.

2003) ("The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of his patent.").

Actelion repeatedly distinguished Veletri from Flolan based on both the use of arginine instead of glycine and the higher pH. The most notable distinction was made in response to the initial rejection of the '802 divisional application based on the term alkalinizing agent:

> The present invention claims a) a pharmaceutical composition comprising epoprostenol or a salt thereof; and b) a stable epoprostenol solution. All of said claims are *limited* in the following way: a) *arginine as alkalinizing agent* is used, b) the pH of the solution is higher than 12, and c) inorganic base from the group consisting of sodium hydroxide and potassium hydroxide are used to reach the high pH.

(Harold Decl., Ex. J, Response Under 37 C.F.R. 1.111 at VELET_00000457 (emphasis added)). The application and the '802 patent itself make clear that the "multiple grounds for distinguishing" Flolan "do[] not immunize each of them from being used to construe the claim language." *Anderson Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1374 (Fed. Cir. 2007). Indeed, the specification in the '802 patent application distinguished even the Flolan formulation after it was adjusted to pH 13, noting that it was not as good as the one with arginine. (*See* Harold Decl., Ex. B, at 14:33 to 37). Further, the terms "alkalinizing agent" and "arginine" are clearly related, as Actelion substituted one for the other during the prosecution, and the use of "alkalinizing agent" in the abstract is clearly a reference to "arginine" in claim 1. (*See id.* at cover; 18:49).

Sanofi v. Watson Labs. Inc., 875 F.3d 636 (2017), is factually distinct from this case. In *Sanofi*, the Court found the plaintiff had not disclaimed a definition while prosecuting a patent for dronedarone, a cardiovascular drug, when it "amended the sole independent claims (hence all claims) so as expressly to exclude pharmaceutical compositions with a 'polysorbate surfactant' from the claims of the '493 patent." *Id.* at 650. Because writing "an express limitation into the claims" was "all that [the plaintiff] did, in prosecuting the [initial] application" and the plaintiff

"did not argue during prosecution that the unamended claim language of the '493 patent, or the disclosed invention generally, excluded polysorbate surfactants," the Court held that the process did "not imply a disclaimer as to the claims, when later issued in the continuation, that lack the first patent's express narrowing limitation." *Id.*

Here, unlike *Sanofi*, Actelion made clear statements distinguishing Veletri from the prior art to overcome an obviousness objection. The examiners in both patents' prosecution objected to claiming "alkalinizing agent" with a broad definition. (*See* Harold Decl., Ex. G, Response to Restriction Requirement at VELET_00000427; Harold Decl., Ex. Q, March 12, 2012 Office Action Summary at VELET_00000109). While the Court notes that these "unilateral statements by . . . examiner[s] do not give rise to a clear disavowal of claim scope," the statements are relevant as "evidence of how one of skill in the art understood the term at the time the application was filed." *Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1347 (Fed. Cir. 2005). Additionally, statements by Actelion during prosecution of the '802 patent distinguished the invention itself, rather than specific claim terms; for example, "The person skilled in the art . . . would be led away from *the present invention*, a high pH epoprostenol formulation *with arginine*." (Harold Decl., Ex. J, Response Under 37 C.F.R. 1.111 at VELET_00000458 (emphasis added)).

In a recent decision, *Sumitomo Dainippon Pharm. Co. v. Emcure Pharm., Ltd.*, No. 18-cv-2065 (SRC), 2018 WL 4906268 (D.N.J. Oct. 5, 2018), a Court in this District drew similar distinctions from *Sanofi* to find prosecution disclaimer had occurred. The Court considered whether the term "pregelatinized starch" should be construed "as limited to a range of 10% to 50% by weight of the preparation." *Id.* at 11. The Court noted that "the applicants, during prosecution of the [parent] patent, argued that *the disclosed invention generally* excluded formulations with pregelatinized starch content under 10%." *Id.* at 17. During prosecution of the parent, the

Sumitomo plaintiffs "took the position that their claims should be allowed because the invention did not cover formulations with pregelatinized starch content under 10%, which appeared in the prior art." *Id.* The prosecution history underlying this action is analogous to those in *Sumitomo*. Based on the arguments made by Actelion in prosecuting the '802 (parent) patent, Actelion was arguing that its claims should be allowed because the invention did not cover formulations using glycine as an alkalinizing agent.

Therefore, by amending the claim language from "alkalinizing agent" to "arginine" and clearly distinguishing the stability of Flolan, even after the pH was adjusted, Actelion made clear that both the pH and the use of arginine distinguished the application from the prior art. In conclusion, the statements by Actelion during the prosecution of the '802 patent constituted a disclaimer of glycine from the definition of alkalinizing agent as used in the '227 patent.[1]

Specifications of the '227 Patent

The specifications in the '227 patent further indicate that arginine is excluded as an alkalinizing agent. Although technically encompassed by the language "any other amino acid with a pKa of 9.0 and above," glycine is not explicitly named. (*See* '227 Patent, at 5:15 to 16). Also, section of the '227 patent discussed a "Comparison of Various Epoprostenol Compositions." (*Id.* at 10:59). In one such comparison (example four), Actelion used "a formulation that [was]

[1] Actelion's statement that the "claims are limited" in that "arginine as alkalinizing agent is used" could be interpreted as restricting the definition of alkalinizing agent to mean only arginine. However, there is no need to adopt such a restrictive definition, primarily because the specifications of the '802 patent indicate that Actelion disclaimed only glycine. The specifications include a similarly broad definition of alkalinizing agent to that provided in the '227 patent:

> The alkalinizing agent may be, but are not limited to, arginine, lysine, meglumine, N-methyl glucosomine, any other amino acid with a pKa of 9.0 and above, alkaline phosphates such as trisodium phosphates, inorganic carbonates such as sodium carbonates, sodium salts of carboxylic acids such as tetrasodium-EDTA or combinations thereof. The most preferred alkalinizing agents are arginine and sodium carbonate.

(Harold Decl., Ex. B, '802 Patent, at 5:4 to 11).

identical to the commercially available Flolan . . . , except that the pH [had] been adjusted." (Ratliff Decl., Ex 1, '227 Patent, at 14:11 to 13). Actelion concluded that Flolan, adjusted to 13 pH, "showed a better stability, but not as good as the mannitol/arginine pH 13 formulation." (*Id.* at 14:33 to 37). Moreover, the analysis of example two showed that "epoprostenol with arginine" was "a significant improvement over the Flolan [solution]." (*Id.* at 8:63; 9:25).

Moreover, the treatment-related claims, which claim "arginine" and not the purportedly broader term "alkalinizing agent." And, Actelion stated in its specifications, "The most preferred alkalinizing agents are arginine and sodium carbonate." ('227 Patent at 5:19-20). These statements in the specification further support that it was both arginine and the high pH that formed the basis of Actelion's patent claims.

Prosecution of the European Union Patent

Sun's citation to the prosecution history of Actelion's European Union patent, during which Actelion stated, "The bulk solution of the present invention differs from the bulk solution from which the Flolan formulation is prepared in that it contains *arginine instead of glycine* as the alkalinizing agent and in that the solution has a pH of 13 or higher instead of below 10.2-10.8." (Harold Decl., Ex. V, Response to Communication of Notices of Opposition to European Patent No. 1,993,557, at 9 (emphasis added)). "'[T]he varying legal and procedural requirements for obtaining patent protection in foreign countries might render consideration of certain types of representations inappropriate' for consideration in a claim construction analysis of a United States counterpart." *TI Group Auto. Sys. (N.A.), Inc. v. VDO N.A., LLC*, 375 F.3d 1126, 1136 (Fed. Cir. 2004) (quoting *Caterpillar Tractor Co. v. Berco, S.p.A.*, 714 F.2d 1110, 1116 (Fed. Cir. 1983)). However, the statements made by Actelion's counsel in prosecuting the EU application were clearly made to distinguish the prior art (Flolan) and therefore are both "relevant and not related

to unique aspects of foreign patent law." *Apple, Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1312-13 (Fed. Cir. 2014) (collecting cases). Therefore, the statement to the European Patent Office further supports Sun's argument that glycine was disclaimed from the definition of "alkalinizing agent" in the '227 patent.

CONCLUSION

For the reasons stated herein, Actelion has made statements in obtaining the '227 patent – in the '227 patent and its prosecution history, the '802 divisional patent and its prosecution history, and its statement to the European Patent Office – which clearly indicate that glycine was not within the scope of its claims. Actelion disclaimed Glycine from the definition of alkalinizing agent by distinguishing the prior art during the prosecution of the divisional '802 Patent; a conclusion bolstered by statements made in the prosecution history of the '227 Patent, the specifications of the '227 patent, and the prosecution history of the corresponding EU patent. As such, the term "alkalinizing agent," as used in the '227 patent, is construed to exclude glycine.

2/15/19

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